Cerebrospinal Fluid Biopterin and Biogenic Amine Metabolites During Oral R-THBP Therapy for Infantile Autism

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Treatment with 6R-L-erythro-5,6,7,8-tetrahydrobiopterin (R-THBP) has been suggested to improve autistic behavior. Cerebrospinal fluid (CSF) levels of total biopterin, oxidized and reduced forms of biopterin, homovanillic acid, and 5-hydroxyindoleacetic acid were measured in 14 autistic children and 18 controls to clarify the mechanism of action of R-THBP. The 14 autistic children received R-THBP orally at 1 mg/kg per day; 7 children showed clinical improvement (responders) and the other 7 patients did not (nonresponders). There were no significant differences between responders, nonresponders, and controls in the CSF levels of the metabolites before R-THBP administration. When lumbar puncture was repeated in 6 autistic children in the 24th week of R-THBP therapy, there was no significant change in the CSF levels of any metabolites.

INTRODUCTION

6R-L-Erythro-5,6,7,8-tetrahydrobiopterin (R-THBP) is a common cofactor in the biosynthesis of neurotransmitters such as catecholamines and serotonin (Scriver, Kaufman, & Woo, 1989) (Figure 1). A deficiency of

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R-THBP results in severe neurological symptoms, which were initially reported as malignant phenylketonuria. R-THBP was synthesized recently, and has been used in the treatment of malignant phenylketonuria (Kaufman, Kapatos, McLnnes, Schulman, & Rizzo, 1982; Scriver, et al., 1989).

Decreased levels of biopterin in the cerebrospinal fluid (CSF) have also been demonstrated in other neurological diseases, such as Parkinson's disease (Curtius, Niederwiese, Levine, & Milder, 1984), depression (Curtius et al., 1983), progressive dystonia with diurnal variation (Fink et al., 1989), and Alzheimer's disease (Kay et al., 1986). In the first three diseases, administration of R-THBP administration has been reported to produce symptomatic improvement.

The etiology of infantile autism is still unknown and no biological markers have been detected. However, some investigators have suggested that infantile autism may be associated with the brain monoaminergic system (Tsai, 1989). Naruse, Hayashi, and Takesada (1992) found a marked decrease in the intestinal transport of deuterated phenylalanine and tryptophan in several patients with typical infantile autism, and postulated that a defect in the cellular transport of aromatic amino acids may at least contribute to the development of autism by decreasing the production of serotonin and catecholamines in the brain.

Based on the above postulate, clinical studied of the effect of R-THBP on autism have been conducted by Japanese researchers. In a double-blind placebo-controlled study, 22 of 41 patients (53.7%) receiving R-THBP orally at a dose of 1 mg/kg per day showed marked or moderate clinical improvement, and improvement was significantly more common in the R-THBP group than in the placebo group, 22/41 (53.7%) versus 13/42 (30.9%), p < .05 (Nakane, Naruse, Takesada, & Yamazaki, 1992).

A multicenter open-label study involving 33 institutions and 136 patients with autism was subsequently conducted. R-THBP was given orally at an initial dose of 1 mg/kg per day and the dose was adjusted in a range of 1-3 mg/kg per day depending on the patients' response. In this larger study, 48.5% of the patients (66/136) showed marked or moderate clinical improvement (Nagahata et al., 1992). It is not known why less than half of these patients responded to R-THBP and the others did not respond.

To further investigate the mechanism by which R-THBP acts in infantile autism, we measured the CSF levels of total biopterin, biopterin fractions, as well as those of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in CSF during treatment with R-THBP.